Evidence and quantitation of left ventricular systolic resistance

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SHROFF, SANJEEV G., JOSEPH S. JANICKI, AND KARL T. WEBER. *Evidence and quantitation of left ventricular systolic resistance.* Am. J. Physiol. 249 (Heart Circ. Physiol. 18): H358–H370, 1985.—Instantaneous left ventricular pressure is a function of both volume (elastic behavior) and flow (resistive behavior). However, a quantitative description of ventricular resistance and its effects on ventricular performance remains to be elucidated. Accordingly, ventricular resistive behavior was studied in six isolated canine hearts. Our experimental findings indicate *1*) for a specified time (t_s), volume (V_s), and contractile state (CS), the ventricular pressure-flow relation was linear (r = 0.96–0.99) within the range of flows examined (0–250 ml/s); *2*) ventricular resistance increased with increments in t_s, V_s, and CS, whereas the zero-pressure flow intercept was invariant; *3*) resistance could be uniquely quantified as a linear function of isovolumetric pressure. In six experiments, the slope of this relationship ranged from 1.1 to 2.1 × 10^{-3} s/ml while the intercept did not differ from zero; and *4*) end-systolic elastance, estimated from end-systolic pressure-volume data, was in substantial error under the conditions of finite (>35 ml/s) end-systolic flows. Finally, the results from a computer simulation of the coupled ventricular-arterial system indicated that ventricular resistance primarily affects the pulsatile nature of aortic flow. The unique isovolumetric pressure-resistance relation suggests that the rate-limiting properties of the contractile process may be causally related to the observed ventricular resistive behavior.

isolated canine heart; systolic mechanical properties; flow-clamp technique; force-velocity relation; systolic elastance

THE OVERALL MECHANICAL PROPERTIES of the left ventricular chamber are in part determined by the mechanical properties of the constituent muscle fibers and the connective tissue network in which they are supported. For example, the relationship between instantaneous ventricular pressure and volume, which reflects the elastic behavior of the chamber, is analogous to the force-length relation of the muscle. This relationship has been studied extensively using a variety of techniques (8, 9, 16, 22, 24–26, 28). Common to each approach has been the observation that, during systole, ventricular elastance gradually increases from its minimum value at end diastole to a maximum at end systole, and thereafter declines during the relaxation phase back to its end-diastolic value. Thus the ability of the myocardium and its left ventricular chamber to generate pressure for a given volume can be phenomenologically described by a time-varying elastance. The relationship between ventricular pressure and flow, or the resistive behavior of the chamber that is analogous to the force-velocity relation of the muscle, has received relatively less attention. In isolated papillary muscle it is clear that instantaneous muscle force is a function of shortening velocity together with contraction time and muscle length (18, 19). It should therefore follow that ventricular flow would be an independent determinant of chamber pressure. Recent studies have shown this to be true (8, 9, 14, 16, 21, 25–27). Differences in definition and mathematical derivation of ventricular resistance, however, have prohibited a uniform consensus as to the magnitude, origin, and importance of chamber resistance. Accordingly, the present investigation was undertaken with the following three objectives in mind: *1*) to provide a quantitative description of ventricular resistance throughout systole; *2*) to assess the influence of resistance on the interrelationship among instantaneous ventricular pressure, volume, and flow, particularly at end systole where elastance is maximum; and *3*) to assess the importance of chamber resistance in determining the systolic performance of the ventricle.

Definition of Ventricular Resistance

Instantaneous ventricular pressure [$P(t)$] is assumed to be a function of four independent variables: time [t] during systole measured from the onset of contraction or QRS complex of the electrocardiogram; chamber volume [$V(t)$]; ventricular flow [$\dot{V}(t)$] or the rate of change of chamber volume; and myocardial contractile state (CS) (8, 16, 27). Accordingly, one can represent pressure in the following functional form

$$P(t) = f[t, V(t), \dot{V}(t), CS] \qquad (1)$$

An inertial component, describing the dependence of pressure on volume acceleration, has been omitted because previous studies (16, 23) have shown it to be negligible in comparison with the elastic and resistive components.

Ventricular resistive behavior is strictly a phenomenological description of the relationship between ventricular pressure and flow. For a given t, $V(t)$, and CS, resistance is defined as the partial derivative of $P(t)$ with respect to $\dot{V}(t)$. By varying flow and observing the changes in ventricular pressure at a fixed t, $V(t)$, and

CS, we are assessing the independent effects of flow on pressure. This definition emphasizes the fact that, during systole, the left ventricle represents a time-varying system (10), and therefore its mechanical properties should be described in the time domain as opposed to the frequency domain. This issue is further elaborated in the DISCUSSION.

METHODS

The flow-clamp technique (27) was chosen to quantify ventricular resistive behavior throughout systole. This method is described in greater detail below. In brief, it consists of producing various ventricular flows at a specified time (t_s) and volume (V_s) in systole (Fig. 1). An isolated heart preparation is the most appropriate choice to create these conditions. The same preparation was also used in conjunction with a servo-control system, described elsewhere (11), to obtain ejecting beats with various ejection pressure contours. These ejecting beat data, along with the results of the flow-clamp studies performed in the same heart, were used to assess the effects of ventricular resistance on chamber dynamics, especially the end-systolic pressure-volume relation. Finally, a computer simulation study was performed to quantify the role of ventricular resistance in determining systolic performance. In that simulation, the left ventricle was represented as a time-varying elastance in series with a pressure-dependent ventricular resistance (15, 16) and was coupled to an arterial load represented by a three-element modified Windkessel (30). Details regarding the simulation study are presented in the APPENDIX.

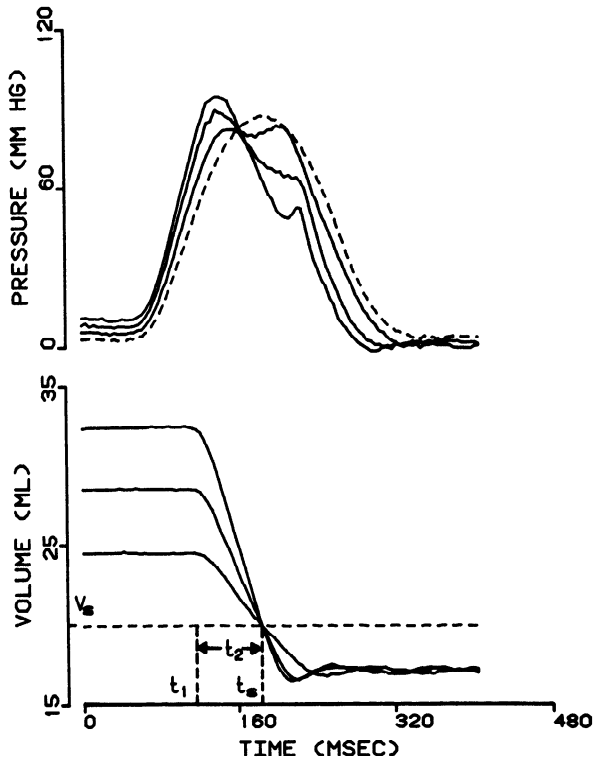


FIG. 1. Typical set of pressure and volume data during a flow-clamp experiment. V_s and t_s, specified volume and time, respectively; t_1, time of initiation of ramp volume change; t_2, time from onset of ramp volume change to t_s.

Biological Preparation and Electromechanical System

To achieve independent and precise control of volume, flow, and contractile state, a servo-regulated, isolated canine heart preparation was used. The biological preparation and electromechanical servo control reviewed briefly herein have been described in detail elsewhere (11).

A total of six experiments was performed. All dogs (23 ± 4 kg) were anesthetized with pentobarbital sodium (25–30 mg/kg iv). In each experiment, the isolated heart was perfused at a constant aortic pressure (100 ± 10 mmHg) using pressurized oxygenated blood from a support dog. Bipolar pacing electrodes sewn to the right atrium were used to control heart rate while leads sewn to the left ventricle were used to monitor the epicardial electrogram. CS was augmented by infusing dobutamine (4–6 μg/min) directly into the aortic perfusion line of the isolated heart.

To measure and control ventricular volume, a compliant latex balloon secured to one end of a metal cannula was placed in the left ventricle via the mitral orifice. The other end of the cannula was coupled to a cylinder with a piston. The whole mechanical system (i.e., the cylinder, cannula, and balloon) was filled with debubbled solution containing 90% ethylene glycol and 10% normal saline. The position of the piston was governed by an electrohydraulic actuator. A linear potentiometer sensed the position of the piston, thus yielding an instantaneous measurement of ventricular volume (resolution 0.2 ml). Both ventricles were vented, and the right ventricle remained empty in all experiments.

Ventricular pressure was measured using a short, stiff Teflon catheter placed in the balloon via a sidearm in the cannula and a Statham pressure transducer (P23Gb). Flow into and out of the balloon was directly measured by an extracorporeal electromagnetic flow probe situated in the line connecting the piston and the balloon. During an experiment, an additional flow signal was obtained by analog differentiation of the volume signal. These two flow signals were continuously displayed on an oscilloscope in the *X-Y* mode. A linear relation between the two signals indicated that the fluid-filled mechanical system was completely debubbled, and the volume signal obtained from the piston position represented the balloon volume without any phase lag. In all of the six experiments reported herein, this was the case, and therefore the two flow signals were identical.

The Flow-Clamp Technique

As discussed earlier, instantaneous left ventricular systolic pressure is a function of the time of observation, the volume and flow at the time of observation, and the contractile state. The flow-clamp technique (27) is one of the experimental methods to evaluate the independent effects of flow on pressure. It consists of producing constant systolic flows (i.e., a linear reduction in volume) of varying magnitudes at a fixed t_s, V_s, and CS (Fig. 1). Thus, by plotting the observed pressure against flow under these circumstances, one can obtain the ventricular pressure-flow relation for a specified t_s, V_s, and CS.

Finally, t_s, V_s, and CS can be varied in a systematic manner to evaluate the effects of each of these parameters on the ventricular pressure-flow relation. In the present study, a custom-made electronic circuit (flow-clamp generator) enabled us to produce different ventricular flows at a specified time and volume in systole. Four parameters could be adjusted (Fig. 1): delay time (t_1), flow duration (t_2) until the time of observation, initial volume (V_i), and specified volume (V_s). It is evident from Fig. 1 that the specified time or time of observation (t_s) is equal to $t_1 + t_2$. The voltage output of this circuit controlled the position of the piston via a closed-loop servo-control system (11). The position of the piston was held constant corresponding to V_i. On command, the flow-clamp generator produced a linear drop in the voltage output beginning at time t_1 measured with respect to the pacing stimulus of the isolated heart. Thus a linear change in ventricular volume (ramp volume change) was obtained. The rate of change of volume [or ventricular outflow, $\dot{V}(t)$, ml/s] was automatically adjusted by the flow-clamp generator according to the following equation

$$dV(t)/dt = \dot{V}(t) = (V_i - V_s)/t_2 \quad (2)$$

Thus, by keeping t_1, t_2, and V_s fixed and varying V_i, a series of contractions having different flows at a specified time and volume can be obtained (Figs. 1–4). In addition, the entire series of ramp volume changes could be repositioned in systole by simply changing t_1 (Fig. 2), and the whole procedure could be repeated for a new observation volume by altering V_s (Fig. 3).

To eliminate the transient effects of a sudden cessation of flow, the linear reduction in ventricular volume was continued beyond t_s for ~10–20 ms. The flow-clamp generator circuit filled the ventricle to V_i three beats after the beat with the volume perturbation.

Experimental Protocol

At the time of initial insertion in the left ventricle, the balloon was totally collapsed. To remove all folds from the balloon wall and to ensure that it conforms to the endocardial surface of the left ventricle, the ventricle was allowed to contract isovolumetrically while the volume was slowly increased over the end-diastolic pressure range of 0–20 mmHg and then decreased to a preset level. Next, four or more sets of isovolumetric pressure-volume data were obtained over the same range of end-diastolic pressure. The slope of the peak isovolumetric pressure-volume relationship was used as an indicator of the CS of the left ventricle (22, 28). To evaluate the constancy of base-line CS, this relationship was again recorded just prior to the pharmacological alteration of CS. Only those data wherein the two slopes (i.e., at the beginning and just prior to pharmacological alteration of CS) of the peak isovolumetric pressure-volume relation were within 5% of each other were used in further analysis.

For a fixed V_s, a set of ventricular pressure-flow relations were obtained for various specified times in systole by varying the parameter t_1 (Fig. 1) so that three to four values of t_s were obtained: 25, 50, 75, and 100% of systolic duration (i.e., from QRS complex to the time of peak isovolumetric pressure). This procedure was repeated for three values of V_s corresponding to isovolumetric end-diastolic pressure of 5, 10, and 15 mmHg, respectively. For every combination of t_s and V_s, six to eight flows were generated by varying V_i (Fig. 1). Steady-state isovolumetric contractions for every V_i were first established, which were then followed by a ramp volume change at an appropriate rate as given by *Eq. 2*. After the flow-clamp studies, pressure, volume, and flow data of ejecting beats were recorded in four of six experiments, corresponding to two end-diastolic volumes (end-diastolic pressure 10 and 15 mmHg), each having three ejection pressure contours, i.e., ever increasing, constant, and ever decreasing. The ejecting beat data were recorded to assess the effects of ventricular resistance on the end-systolic pressure-volume relation.

Finally, dobutamine, a synthetic catecholamine, was infused (4–6 μg/min) into the aorta of the isolated heart to enhance CS. The entire procedure outlined above was repeated for the new CS. To ensure constancy of heart rate during control and enhanced CS, the heart was paced at a rate 10–15 beats/min higher than the minimum capture rate (132 ± 16 beats/min) under the control CS.

Data Acquisition and Analysis

All analog data were directly digitized using a PDP 11/34 computer at 240 Hz with 10-bit resolution. For the flow-clamp studies, three beats were recorded, i.e., a steady-state isovolumetric beat with volume V_i, followed by a beat with ramp volume change, followed by an isovolumetric beat with volume slightly below V_s (since volume withdrawal continued beyond t_s). For the ejecting beats, three steady-state contractions were digitized and stored. For all measurements, the QRS complex of the epicardial ECG was used to determine *time zero*. The simulation study was performed using the PDP 11/34 computer.

In the present study the statistical analysis primarily involved simultaneous comparison of a number of pressure-flow relations (2 or more, typically 4). Since these relations were found to be linear (see below), analysis of covariance was first used to assess if there was a difference among these relations (17). If a difference was found, a linear regression model using groups as dummy variables was used to identify whether the slope or intercept or both were different (7). All statistical analyses were performed using the BMDP statistical software (University of California, Berkeley) implemented on a PDP 11/44 computer. The differences were regarded as significant only when $P < 0.05$.

RESULTS

Quantitation of Ventricular Resistance

A typical set of pressure-volume data obtained during a flow-clamp study is shown in Fig. 1. The broken lines represent data corresponding to an isovolumetric beat where ventricular volume was held constant at V_s (20.0 ml in this example). The remaining three contractions

began with successively higher end-diastolic volumes or V_i's (23.9, 27.9, and 32.0 ml). However, the reduction in volume proceeded at a rate (see *Eq. 2*) that ensured the attainment of the specified volume (V_s 20.0 ml) at the specified time (t_s 183 ms) for all contractions. It can be seen from Fig. 1 that, even though t_s and V_s are identical,ventricular pressure at t_s and V_s declines progessively as ventricular outflow is increased. This clearly establishes ventricular flow as an independent determinant of ventricular pressure.

Effect of time on ventricular resistive behavior. In Fig. 2 two sets of data are presented to illustrate the effects of varying specified time, early in systole, (top left panel, t_s 131 ms) and late in systole (top right panel, t_s 183 ms). For the sake of clarity, only four of eight contractions with different flows are depicted for each of the two times. Note that V_s (24.7 ml) is the same for both sets of contractions and that the dependence of pressure on flow is evident at both times. The corresponding pressure-flow relations (i.e., for V_s 24.7 ml) are plotted in the bottom panel of Fig. 2. The solid lines correspond to the linear regression lines, each computed from all eight data points, and the symbols represent the data shown in the upper panels. Two salient features regarding these pressure-flow relations were apparent. First, both relations were linear (r = 0.99 and 0.98, respectively) over the range of flows investigated (0–193 ml/s) and second, the rate of decline in pressure for a given flow (i.e., the negative slope of these relations or ventricular resistance) was higher (P = 0.003) for a higher t_s (0.0987 vs. 0.1735 mmHg·s·ml^{-1}). The extrapolated zero pressure-flow intercept (V_{max}) decreased slightly (801 to 728 ml/s) as t_s was increased; however, the decline did not reach statistical significance (P = 0.289). The above statistical inferences were based on the simultaneous comparison of three observation times (t_s = 80, 131, and 183 ms). The slope and zero-pressure intercept for t_s = 80 ms (not shown in Fig. 2) were 0.0410 mmHg·s·ml^{-1} and 816 ml/s, respectively.

Effect of volume on ventricular resistive behavior. Figure 3 illustrates two sets of data corresponding to identical t_s (183 ms) but different V_s (20.0 and 24.7 ml, respectively). As before, only four of eight contractions for each V_s are shown. The corresponding pressure-flow relations (i.e., for t_s 183 ms) are depicted in the bottom panel of Fig. 3. The solid lines are the regression lines fitted to all eight data points for each V_s. Once again both relations were found to be linear (r = 0.99). The

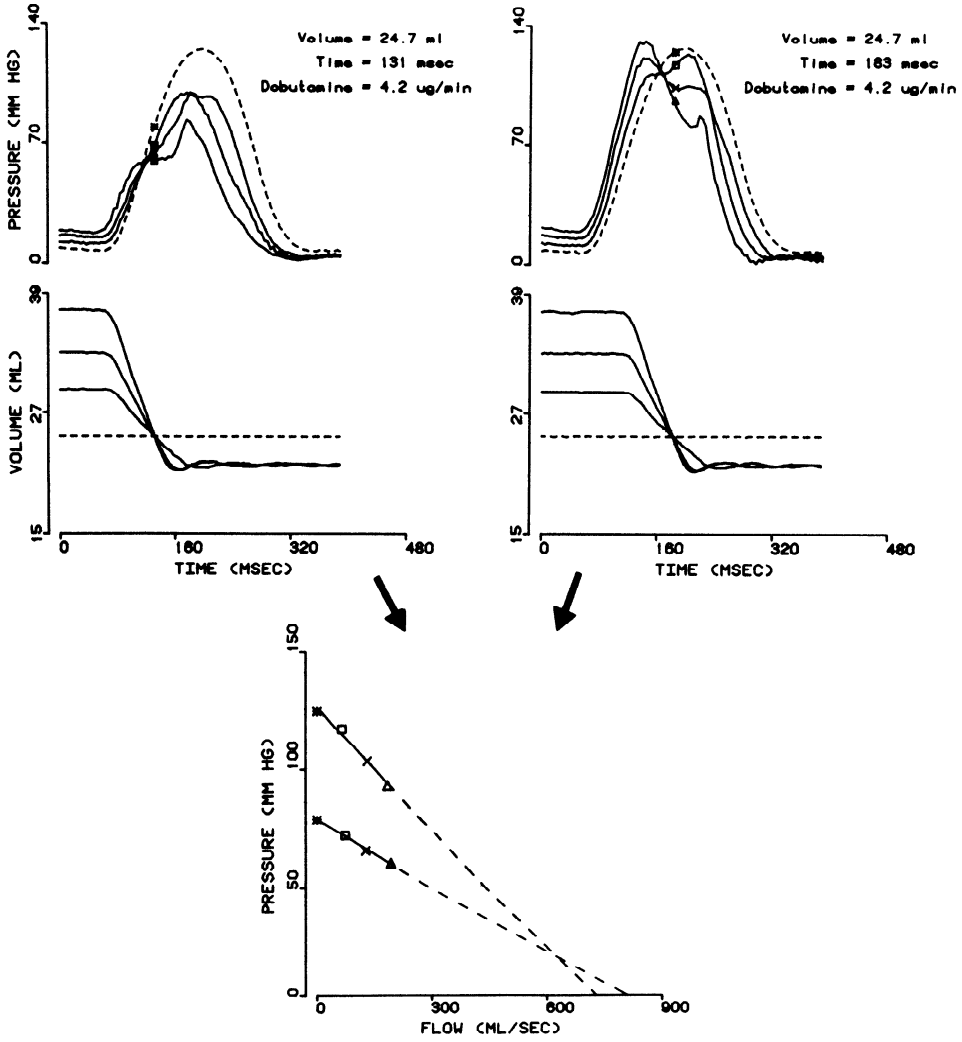


FIG. 2. Ventricular pressure and volume data (*top panel*) wherein different flows are produced at a fixed specified volume and contractile state while specified time is varied (*top left* vs. *top right*). *Bottom panel*: corresponding pressure-flow relations. Line with greater absolute slope represents data for higher value of specified time.

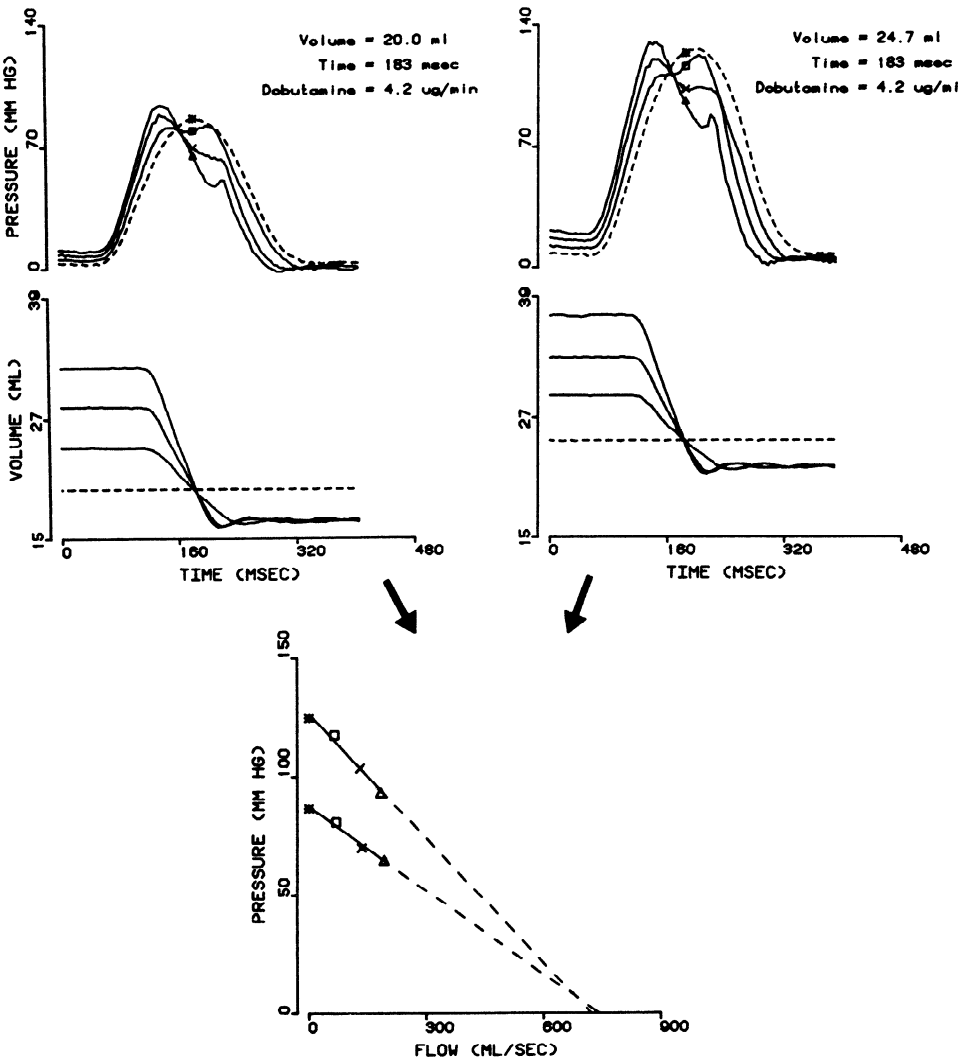


FIG. 3. Ventricular pressure and volume data (*top panel*) wherein different flows are produced at a fixed specified time and contractile state while the specified volume is varied (*top left* vs. *top right*). *Bottom panel*: corresponding pressure-flow relations. Line with greater absolute slope represents data for higher value of specified volume.

negative slope of the relation corresponding to the higher volume was significantly greater ($P = 0.004$) than the other relation (0.1175 vs. 0.1735 mmHg·s·ml^{-1}), whereas V_{max} values were statistically not different from each other (741 vs. 728 ml/s, $P = 0.376$). The above statistical inferences were based on the simultaneous comparison of three observation volumes (V_s = 20.0, 24.7, and 28.0 ml). The slope and zero-pressure intercept for V_s = 28.0 ml (not shown in Fig. 3) were 0.2120 mmHg·s·ml^{-1} and 719 ml/s, respectively.

Effect of contractile state on ventricular resistive behavior. CS was augmented by infusing dobutamine (4–6 μg/min). The rate of infusion was titrated to yield at least 50% increase in the slope of the peak isovolumetric pressure-volume relation. The effects of augmenting CS (4.2 μg/min of dobutamine) on ventricular resistive behavior are shown in Fig. 4. As above, only four of eight contractions with different flows are depicted for each of the two CSs. V_s and t_s were kept constant at 20 ml and 183 ms, respectively. Once again, both pressure-flow relations were linear (r = 0.97 and 0.99, respectively), and the negative slope of the relation for augmented contractile state was higher ($P = 0.001$) than that of the control (0.0799 vs. 0.1175 mmHg·s·ml^{-1}), whereas V_{max} was statistically not different (774 vs. 741 ml/s, P = 0.201).

These results can be summarized as follows. Ventricular resistance increases with increments in the time of observation (t_s), with larger chamber volume (V_s) at the time of observation, and with augmentation in CS. It is well known that ventricular isovolumetric pressure depends on t_s, V_s, and CS in an exactly similar manner. Therefore, we plotted ventricular resistance against the corresponding isovolumetric pressure (i.e., pressure at zero flow on the pressure-flow relations) for 16 combinations of t_s, V_s, and CS obtained in *experiment 3* (Fig. 5). Data presented in Figs. 2–4 are included in Fig. 5. This relation was found to be linear (r = 0.987) with slope and intercept values of 0.00145 (±0.00014) s/ml and −0.015 (±0.0128) mmHg·s·ml^{-1}, respectively. The intercept was statistically not different from zero.

Similar results were obtained in all six experiments. Table 1 summarizes the slope and the intercept values of the ventricular resistance-isovolumetric pressure relations for all six experiments. The slope values ranged from 0.00110 to 0.00210 s/ml, and the intercepts were statistically not different from zero (Table 1). Thus we conclude that ventricular resistance at any combination

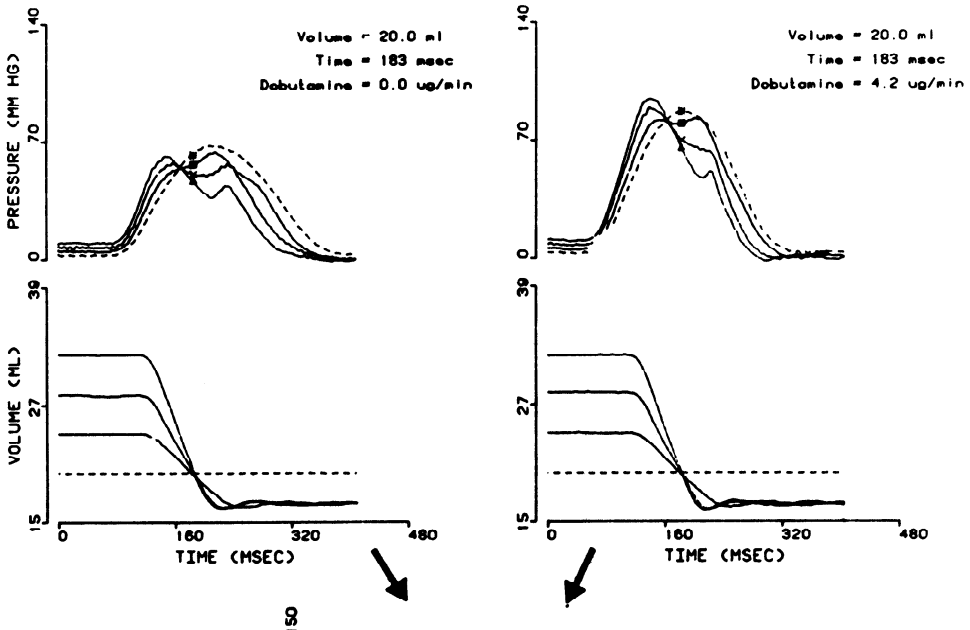
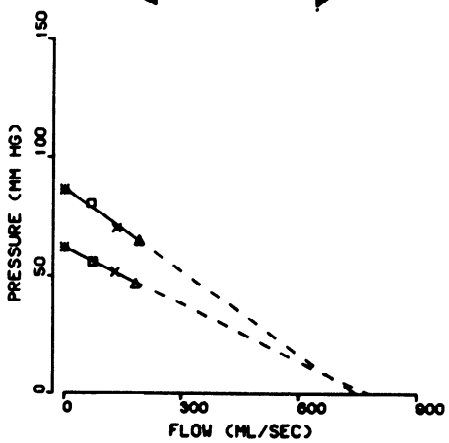


FIG. 4. Ventricular pressure and volume data (*top panel*) wherein different flows are produced at a fixed specified time and volume while contractile state is varied (*top left* vs. *top right*). *Bottom panel*: corresponding pressure-flow relations. Line with greater absolute slope represents data for augmented contractile state.



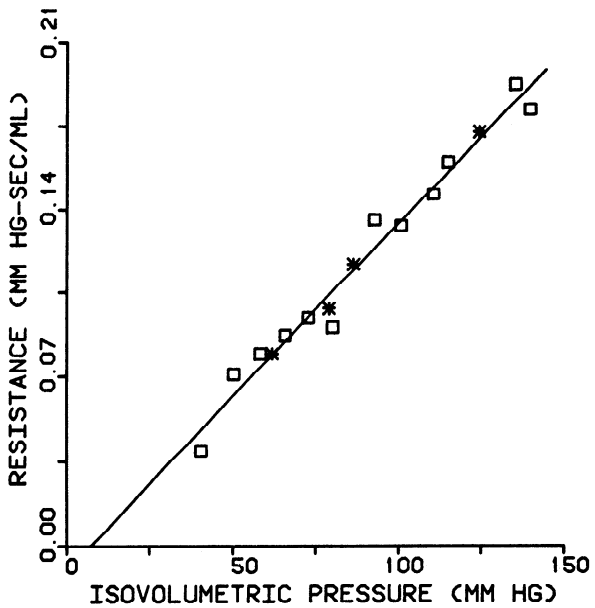


FIG. 5. Ventricular resistance (i.e., negative slope of pressure-flow relations) is plotted against corresponding [i.e., for volume (V_s), time (t_s), and same contractile state] isovolumetric pressure for 16 combinations of V_s, t_s, and contractile state in *experiment 3*. Four *asterisks* correspond to data depicted in Figs. 2–4. *Solid line* corresponds to linear regression line (see text).

TABLE 1. *Summary of results from all experiments: resistance-pressure relationship*

Experiment No.	Slope, s/ml	Intercept, mmHg·s·ml^{-1}
1	0.00142 (±0.00017)	−0.0079 (±0.0158)
2	0.00186 (±0.00036)	0.0086 (±0.0112)
3	0.00145 (±0.00014)	−0.0105 (±0.0128)
4	0.00177 (±0.00028)	0.0037 (±0.0108)
5	0.00210 (±0.00095)	0.0070 (±0.0138)
6	0.00110 (±0.00042)	0.0112 (±0.0287)

95% Confidence limits given in parentheses.

of time, volume, and CS is uniquely related to the corresponding (i.e., for the same time, volume, and CS) isovolumetric or zero-flow pressure.

Effect of Ventricular Resistance on Ventricular Dynamics

It is clear from the results presented above that the effect of ventricular resistance is to reduce ventricular

pressure in comparison with the value that would have existed for the same time, volume, and CS, but with zero flow. The contribution of resistive behavior to ventricular pressure is dependent on the instantaneous flow and the magnitude of resistance. We can relate instantaneous ventricular pressure [$P(t)$] of an ejecting beat to the corresponding isovolumetric pressure [P_0] and the pressure drop due to resistive behavior in the following manner

$$P(t) = P_0 - R(P_0)\dot{V}(t) \quad (3)$$

where $R(P_0)$ is the pressure-dependent ventricular resistance and $\dot{V}(t)$ is the instantaneous ventricular outflow. The results from the flow-clamp studies have shown that $R(P_0)$ can be represented as a linear function of P_0 with zero intercept [i.e., $R(P_0) = K P_0$]. Therefore, *Eq. 3* can be rewritten as

$$P_0 = P(t)/[1 - K\dot{V}(t)] \quad (4)$$

Thus we can compute P_0 (i.e., purely elastic behavior) from the pressure and flow data of an ejecting beat and K (i.e., slope of resistance-pressure relationship). Consider an example where peak flow is 100 ml/s and the corresponding ventricular pressure is 100 mmHg. The results presented above and in previous studies (9, 16) indicate that the average value of K for normal canine hearts is 0.0015 s/ml. Therefore, from *Eq. 4*, the elastic component (P_0) will be 117.7 mmHg, whereas the resistive component [$= K P_0 \dot{V}(t)$] is 17.7 mmHg. Thus the resistive component is 15% of the elastic component in this example.

The effect of resistive behavior on the end-systolic pressure-volume relation is of interest because this relation is used as an approximation of the peak isovolumetric pressure-volume relation, which in turn is a sensitive indicator of ventricular CS (22, 28). After the completion of the flow-clamp studies, we recorded ejecting beat data in four experiments with controlled ejection pressure contours: ever increasing, isobaric, and ever decreasing. Data were recorded at two end-diastolic volumes (end-diastolic pressures of 10 and 15 mmHg). To be consistent in the identification of end systole, we defined end systole as the point in time where the pressure-to-absolute volume (not effective volume, which is equal to absolute volume minus dead volume) ratio was maximum. Figure 6 illustrates the upper portions of the three pressure-volume loops with constant end-diastolic volume (41 ml) and different ejection pressure contours. The symbols (X) represent respective end-systolic points. The solid line BC corresponds to the experimentally obtained peak isovolumetric pressure-volume relation. It is evident that the end-systolic points for the two beats with ever-increasing and constant ejection pressure contours fall on the peak isovolumetric pressure-volume relation (line BC) while the end-systolic point of the beat with ever-decreasing ejection pressure falls short. The beat with ever-decreasing ejection pressure has end-systolic flow of 125 ml/s compared with 0 and 16 ml/s for the other two cases. Nevertheless, one can fit a linear regression line (line B′C′) to the three end-systolic pressure-volume points and obtain incorrect values of slope (E_{max}) and

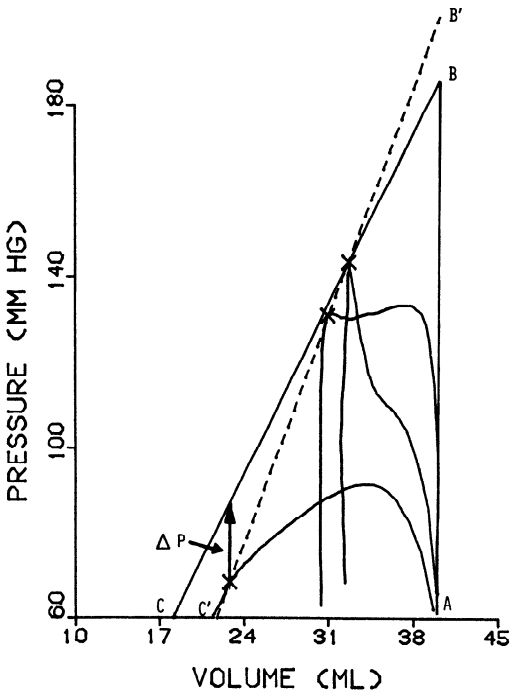


FIG. 6. Three pressure-volume loops (only top portions) are illustrated for ejecting beats with a constant end-diastolic volume (41 ml) but with different ejection pressure contours: ever-increasing, isobaric, and ever-decreasing. Symbols (X) represent end-systolic points. *Lines AB* and *BC* represent isovolumetric pressure-volume loop for same end-diastolic volume and experimentally obtained peak isovolumetric pressure-volume relation, respectively. Linear regression line through end-systolic points (*line B′C′*) is also shown. ΔP, pressure difference at end systole mainly due to resistive component (see text).

intercept (V_d): E_{max} = 6.2 mmHg/ml, Vd = 12.1 ml. The correct values from line BC are 5.7 mmHg/ml and 7.4 ml, respectively. Thus the crucial point, in an attempt to quantify the contractile state of the ventricle from the end-systolic pressure-volume relation, is not whether the end-systolic points lie on a straight line but whether they lie on the corresponding peak isovolumetric pressure-volume line.

It is of interest to know how much of the pressure difference (ΔP) in Fig. 6 can be explained by the resistive component (i.e., flow related). For this purpose, the measured ΔP was compared (Fig. 7) with the predicted ΔP {$= K P(t)\dot{V}(t)/[1 - K \dot{V}(t)]$ from *Eq. 4*} using the data from the four experiments. The results from the flow-clamp studies of each experiment provided the respective K values. The solid line in Fig. 7 is the line of identity, and the broken line corresponds to the linear regression line (r = 0.97). The slope and intercept of the regression line were 0.79 and 0.82 mmHg, respectively. It can be noted from Fig. 7 that the predicted ΔP consistently underestimated measured ΔP for high values of ΔP (>12 mmHg), indicating that mechanisms in addition to elastic and resistive behavior are operative at high ΔP. This issue is further elaborated in the DISCUSSION.

Effect of Ventricular Resistive Behavior on Ventricular Performance

The above results have shown that the magnitude of canine left ventricular resistance is about 0.15 mmHg·

$s \cdot ml^{-1}$ at 100 mmHg. In contrast, the peripheral resistance in normal dogs at rest is 2.5–3.3 $mmHg \cdot s \cdot ml^{-1}$ (30). Therefore, intuitively, it would appear that ventricular resistance may not influence overall ventricular performance (e.g., stroke volume) significantly. We performed a computer simulation study to assess the effects of ventricular resistance on the performance of the left ventricle coupled to its arterial load. The details of the relevant equations, parameter values, and the computation procedure are given in the APPENDIX. The simulation was performed with and without ventricular resistance for every arterial load while keeping end-diastolic volume, heart rate, and ventricular elastance constant.

Ventricular pressure, volume, and flow data are depicted in Fig. 8 for one of the nine combinations of arterial load parameters (*condition 1* in APPENDIX, Table 3). The solid lines represent data for simulation without resistance while the broken lines correspond to the data with resistance. Table 2 lists the mean aortic pressure, stroke volume, ejection time, and peak aortic flow for all nine arterial loads, both with and without resistance. It was observed that the mean aortic pressure and stroke volume decreased only slightly (range 2.8–7.1% for stroke volume and 3.1–11.0% for mean aortic pressure) when the ventricular resistance was included in the simulation. However, the decline in the magnitude of the peak flows was disproportionately greater; the simulation with resistance had considerably lower values of peak flows (31–70%). To quantify the effect of ventricular resistance on the pulsatile nature of flow, a normalized pulse factor (PF) was defined as follows

$$PF = \text{peak flow } (\dot{V}_{max})/\text{average flow } (\dot{V}_{avg}) \quad (5)$$

where $\dot{V}_{avg}$ is stroke volume/T, and T is duration of cardiac cycle. It is evident from Table 2 that by including ventricular resistance in the simulation, the pulse factor was reduced by amounts varying from 26.9 to 62.1%. This reduction was significantly higher than the stroke volume reduction (2.8–7.1%). Therefore, it can be concluded that ventricular resistance primarily affects the

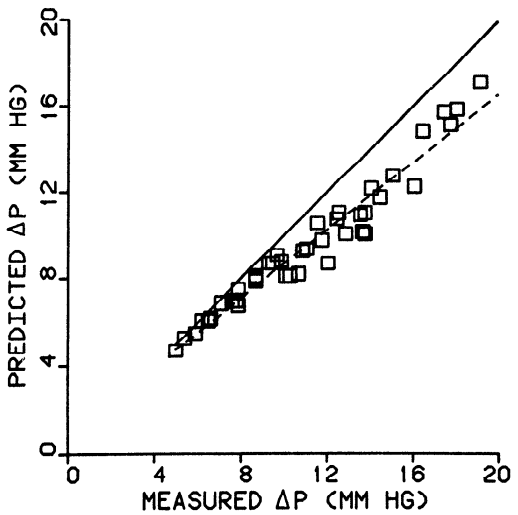


FIG. 7. Predicted pressure difference (ΔP) between end-systolic pressure and corresponding isovolumetric pressure is plotted against measured value. *Solid line* and *broken line* correspond to line of identity and linear regression line, respectively.

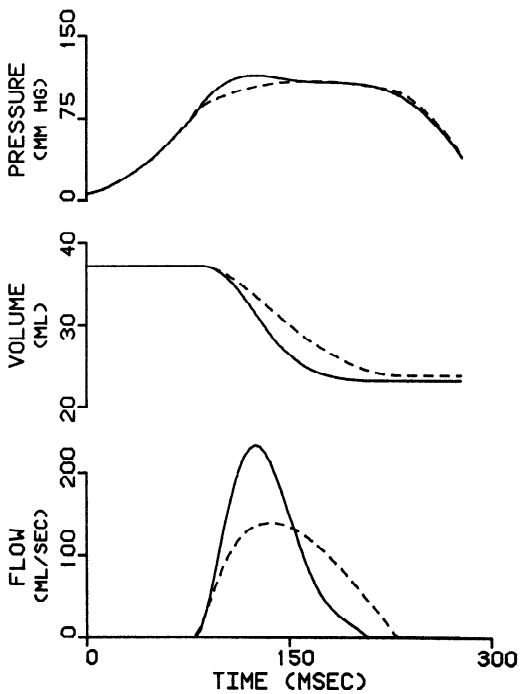


FIG. 8. Instantaneous left ventricular pressure, volume, and flow obtained in computer simulation study (*run no. 1*, Table 3). *Broken* and *solid lines* correspond to simulation results with and without ventricular resistance, respectively.

TABLE 2. *Simulation results*

Run No.	With Resistance					Without Resistance					ΔSV, %	ΔMAP, %	ΔPF, %
	MAP, mmHg	SV, ml	ED, ms	Q_{max}, ml/s	PF	MAP, mmHg	SV, ml	ED, ms	Q_{max}, ml/s	PF			
1	92	13.2	152	139	5.06	96	13.8	130	232	8.04	4.5	4.3	58.9
2	121	8.6	126	106	5.93	130	9.1	94	181	9.60	5.8	7.4	61.9
3	64	17.9	178	170	4.55	66	18.4	164	263	6.85	2.8	3.1	50.5
4	84	11.8	168	117	4.74	87	12.2	156	170	6.70	4.1	3.6	41.4
5	115	7.8	136	95	5.81	119	8.1	120	151	8.94	3.8	3.5	53.9
6	57	16.0	210	125	3.75	59	16.5	202	164	4.76	3.1	3.5	26.9
7	91	14.0	154	149	4.99	98	15.0	114	254	8.09	7.1	7.7	62.1
8	118	9.4	130	113	5.77	131	10.0	94	193	9.31	6.4	11.0	61.4
9	68	18.6	170	179	4.61	71	19.2	138	295	7.37	3.2	4.4	59.9

Run numbers correspond to different combinations of arterial load as listed in Table 3 (APPENDIX). MAP, mean aortic pressure; SV, stroke volume; ED, duration of ejection; Q_{max}, maximum flow; PF, pulse factor (maximum flow/average flow); ΔMAP, %change in MAP; ΔSV, %change in SV; ΔPF, %change in PF. %Changes are with respect to condition with resistance.

pulsatile nature of flow, whereas its effects on mean aortic pressure and stroke volume are minimal.

DISCUSSION

Critique of the Flow-Clamp Technique

The flow-clamp technique, developed by Vaartjes et al. (27), was used to quantify ventricular resistance. It was assumed that ventricular pressure is determined by time, instantaneous volume and flow, and the CS of the left ventricle. Therefore, by keeping time, volume, and CS constant while varying flow, one could characterize the effects of ventricular flow on pressure. Hunter et al. (9) have shown that there are two additional factors that may affect ventricular pressure, i.e., the volume-influence factor and the deactivation factor due to length changes. The volume-influence factor describes the variable effect of changes in ventricular volume on pressure depending on whether the changes are made early or late in systole. Briefly, ventricular pressure is more sensitive to changes in volume early in systole compared with changes late in systole. This may result in an underestimation of ventricular resistance for observation times late in systole because ventricular pressure will drop by a lesser amount for a given change in volume. The deactivation effect due to length changes (1, 12) dictates that, for a given volume and time, ventricular pressure will be smaller following volume changes compared with the value under steady-state condition (i.e., no volume change). Hunter et al. (9) have shown the deactivation component to increase with time during systole, with a maximum decline in pressure occurring *after* peak isovolumetric pressure (Fig. 2 of Ref. 9). Since the drop in ventricular pressure with respect to the isovolumetric condition will be higher due to deactivation, ventricular resistance may be overestimated. It should be noted that both these phenomena (i.e., volume-influence factor and deactivation) are most significant late in systole, and they affect the calculation of resistance in mutually opposite directions. Therefore, the results obtained from the flow-clamp technique may not be in significant error. This is supported by the close quantitative agreement between the present results and the results of Hunter et al. (9), who utilized flow-pulse technique and considered both the volume-influence factor and the deactivation factor in their computations (see below).

Comparison with Other Methods

Templeton et al. (25, 26) have reported a viscous element for the left ventricle that varied linearly with ventricular pressure. This linear relationship was not altered by variations in volume or catecholamine stimulation. These observations are qualitatively similar to our results; however, due to methodological differences, a quantitative comparison is difficult.

Elzinga and Westerhof (5, 6) have examined the mean internal impedance of the left ventricle averaged over the entire cardiac cycle. They defined internal "resistance" of the ventricle as the ratio of mean left ventricular pressure and mean aortic flow. It should be emphasized that this definition of ventricular resistance is different from the instantaneous resistance as defined in this report and by Hunter et al. (8, 9). Average impedance appears to be associated with the time integral of ventricular elastance (29) and is also expected to include the resistive behavior as defined herein. Furthermore, the averaging process eliminates the discriminating information available from the pulsatile nature of the system, and the use of impedance analysis for a time-varying system has been questioned (10).

Suga et al. (21) have reported that the instantaneous ventricular pressure for an ejecting beat was smaller than the corresponding (i.e., for same volume and time) isovolumetric pressure. From their statistical model and experimental data one can compute the coefficient of proportionality for the flow dependence of pressure to be 0.0014 s/ml. This coefficient is mathematically equivalent to the slope of the resistance-pressure relationship presented in this report, and its magnitude is comparable with the slope values listed in Table 1.

Hunter et al. (8, 9) have used the flow-pulse response of an isovolumetrically beating, isolated canine heart to characterize the systolic mechanical properties of the left ventricle. Their calculation of ventricular resistance was not based on any a priori model, and they accounted for both the deactivation and volume-influence factors in the computation procedure. Their results indicated that ventricular resistance was linearly related to isovolumetric pressure, and the slope of this relationship averaged 0.00107 (range 0.00076–0.00134), whereas the intercept was statistically not different from zero. These values are quite similar to those listed in Table 1 and support our contention that the volume influence factor and deactivation, ignored in the present computational technique, may cancel each other.

Vaartjes et al. (27) have also demonstrated the existence of a pressure-dependent left ventricular resistance in isolated rabbit hearts. The slope of the resistance-pressure relationship in these hearts was found to be 0.0426 ml/s, which is comparable to the values obtained for canine hearts in this study (Table 1) and by Hunter et al. (10) when one takes into account the differences in average ventricular volumes (1 vs. 35 ml).

Campbell et al. (3) attempted to predict the instantaneous right ventricular pressure on the basis of a model of right ventricular dynamics. They observed that predictive ability of the model improved significantly with inclusion of a constant series resistance in the model. Ringo et al. (14) have arrived at a similar conclusion while studying left ventricular dynamics. All of the above observations support our contention that the left ventricle exhibits a significant resistive behavior during systole.

Ventricular Resistance-Pressure Relation and its Physical Basis

The results of the present study indicated that for any combination of time, volume, and CS, the ventricular pressure-flow relation was linear over the range of flows

studied (0–250 ml/s). The slope of this linear relation increased in a systematic manner with increments in either the time of observation or the chamber volume at the time of observation or the CS. The extrapolated maximum flow (or zero-pressure flow intercept) was statistically independent of variations in time, volume, and CS. However, it should be noted that the magnitude of the extrapolated maximum flow was four to five times higher than experimentally produced maximum flows, which makes the statistical test rather insensitive in detecting small differences in extrapolated maximum flows. Thus, even though there was a tendency for maximum flow to decline with increments in specified time, the decline did not reach statistical significance.

At this point it is appropriate to compare the maximum extrapolated flow ($\dot{V}_{max}$) at zero pressure (Figs. 2–4) to maximal (or unloaded) velocity of muscle shortening (V_o obtained in papillary muscle experiments. A recent study by Martyn et al. (13) indicates that V_o declines with increments in time of observation and/or reduction in the segment length at the time of observation. In addition, increasing inotropic state by increased extracellular Ca^{2+} has been shown to increase V_o in papillary muscle studies (13, 19). These results are different from those observed for $\dot{V}_{max}$ in the present study. The major reason for this discrepancy may be due to the methodological differences. In most of the papillary muscle studies, including that of Martyn et al. (13), load clamps using quick release were imposed, and the velocity of shortening was measured as a consequence of the load clamp. In the present study and the study of Hunter et al. (8, 9), velocity or flow was the input signal while the effect on pressure was measured as a consequence of flow clamp. We feel that to study the effects of velocity or flow on force or pressure, the input or forcing function should be velocity or flow. Daniels et al. (4) have utilized an "isovelocity release" technique to obtain sarcomere force-velocity relations using trabeculae from rat right ventricle. Their results indicated that *1*) V_o was independent of sarcomere length above 1.86 μm (it should be noted that the normal operating range of sarcomere length was 2.0–2.4 μm); *2*) during the initial phase of systole (i.e., 20–25% of systolic period), V_o rose to a maximum and thereafter was independent of time; and *3*) V_o was independent of the extracellular Ca^{2+} concentration above 1.2 mM. The Ca^{2+} concentration in our blood-perfused preparation was approximately 2.0–2.5 mM. Thus, in contrast to other isolated muscle studies, the observations of Daniels et al. (4) provide support to the results presented in this report.

Ventricular resistance (i.e., the negative slope of the pressure-flow relation) was uniquely determined by the corresponding isovolumetric perssure (i.e., zero-flow pressure), irrespective of the way in which the changes in isovolumetric pressure were created. The relationship between ventricular resistance and isovolumetric pressure was linear with slopes ranging from 0.00110 to 0.00210 s/ml in the six experiments reported here, while the intercept was statistically not different from zero. In our previous report (16), we had represented ventricular resistance for ejecting beats to be a linear function of "instantaneous" ventricular pressure. This was based on our observations on the pulse response of *isovolumetrically* beating, isolated canine hearts (8, 9, 16), in which the instantaneous and isovolumetric pressures were identical. Since the proportionality of ventricular resistance to instantaneous pressure was imposed a priori, the parameter estimation procedure was unable to assess the validity of this assumption for ejecting beats. However, direct experimental evidence presented in this study indicates that the pressure-flow relations for ejecting beats (i.e., the flow-clamped beats) are linear over the range of flows assessed, and therefore, it is appropriate to relate ventricular resistance to isovolumetric pressure and not to instantaneous pressure.

We have described the dependence of ventricular pressure on flow in a phenomenological manner and termed this ventricular resistive behavior. We believe that the rate-limiting properties of the contractile process are causally related to the observed resistive behavior of the intact left ventricle. This is supported by the following observations: *1*) inasmuch as the isovolumetric pressure for a given volume, time, and CS represents the active state of the contractile apparatus, the unique dependence of resistance on pressure indicates that the origin of resistance is closely coupled to the contractile process itself; and *2*) the extrapolated maximum flow ($\dot{V}_{max}$ or flow for zero pressure in Figs. 2–4) is mathematically equivalent to the inverse of the slope (i.e., K in *Eq. 4*) of the resistance-isovolumetric pressure relationship because the intercept of this relationship is zero (Table 2). This can be derived from *Eq. 4* by computing $\dot{V}(t)$ with $P(t)$ equal to zero. Our results indicate that catecholamine stimulation does not alter maximum flow. As previously noted by Hunter et al. (9), this is consistent with the concept that catecholamines improve contractility primarily by altering excitation-contraction coupling (20) and not by increasing the intrinsic rate of contractile reactions. Therefore, we feel that the intrinsic rate of contractile reactions may be one of the determinants of the observed resistance-isovolumetric pressure relationship.

It should be noted, however, that the shortening properties of the contractile process are not the only factors affecting the slope of the resistance-pressure relationship. Large differences in ventricular volume, especially across species (e.g., rabbit vs. dog), result in a significant variation of the slope. This is intuitively reasonable because the same velocity of fiber shortening corresponds to larger flow rates when the ventricle contracts from a larger volume. Second, it is possible that the extracellular components (e.g., collagen) may contribute to ventricular pressure-flow relations; however, their relative contribution is unknown. Finally, shearing forces between myocardial fibers and geometric deformation may also contribute to ventricular resistive behavior (21).

Effects of Resistance on Ventricular Dynamics and Performance

Ventricular resistance reduces the instantaneous chamber pressure in comparison to the value that would have existed for zero flow condition. This reduction could be as high as 15–20% at the time of peak flow. Further-

more, for those conditions wherein substantial flow exists at end systole (e.g., aortic and/or mitral regurgitation), the end-systolic pressure-volume relation will not approximate the peak isovolumetric pressure-volume relation. On the basis of our observations on the magnitude of canine left ventricular resistance, we conclude that the end-systolic flow has to be less than 35 ml/s to keep the error in end-systolic pressure below 5%.

It was noted earlier, based on the data presented in Fig. 7, that for large values of pressure deficits (>12 mmHg) at end systole the predicted values on the basis of ventricular resistance were consistently smaller than the measured ones. Large pressure deficits were always associated with marked unloading (similar to ever-decreasing ejection pressure contour in Fig. 6), high stroke volumes, and substantial flow during the relaxation phase of contraction. This difference may be due to the deactivation factor, which reduces ventricular pressure in proportion to the amount of shortening or stroke volume and which is significant in the relaxation phase (9). Thus, even though elastance and resistance are the two major determinants of instantaneous ventricular pressure, there are other factors that are operative. These include deactivation due to shortening and the volume influence factor (9). As discussed before, these two factors affect ventricular pressure in mutually opposite directions and therefore may cancel each other under normal conditions. However, a systematic study evaluating their relative magnitudes and temporal patterns is necessary.

The results from the computer simulation of the coupled ventricular-arterial system indicated that, for normal canine left ventricles, ventricular resistance has minimal effects on mean arterial pressure and stroke volume. However, the pulsatile nature of flow is markedly altered. Similar conclusions were drawn by Campbell et al. (2), who utilized informational analysis to study the left ventricular-systemic arterial interaction.

Potential Usefulness of Quantitating Ventricular Resistive Behavior

In view of the observation that ventricular resistance does not affect average ventricular performance in terms of stroke volume and mean arterial pressure under normal circumstances, the usefulness of quantitation of ventricular resistance may be questioned. However, we feel that quantifying ventricular resistive behavior along with elastic behavior is useful for the following reasons: *1*) the slope of resistance-pressure relationship may be correlated with the intrinsic rate-limiting processes of the contractile process. As a result, this property will be an additional parameter (along with elastance) with which to describe the state of the myocardium; *2*) the contribution of ventricular resistance in various pathological states that are accompanied by structural (e.g., collagen concentration) and/or biochemical alterations (e.g., isomyosin composition) may be significant; *3*) the results of the present study indicate that the relative contribution of ventricular resistive behavior can be as much as 15–20% of the elastic component at the time of peak flow. Therefore, any model of ventricular systolic dynamics that attempts to relate ventricular pressure to volume and flow throughout systole, as opposed to a specific instance in systole (e.g., end systole), must take into account the resistive behavior. One of the practical advantages of such an approach is that one can make use of the wealth of information that is available throughout systole. Moreover, it is possible to compute ventricular elastance and resistance from pressure, volume, and flow data obtained over a *single* cardiac cycle without any perturbations of the loading conditions (16).

In summary, the left ventricular chamber exhibits a significant resistive behavior (i.e., dependence of ventricular pressure on flow, independent of time and volume) during systole. This behavior can be characterized by the linear relation between ventricular resistance and isovolumetric pressure. The slope of this relation is independent of variations in time, volume, and contractile state. However, large variations in chamber volume, as may be seen between species, can alter this relationship. Finally, further studies are needed to evaluate the relative contribution of contractile apparatus (e.g., cardiac isomyosins), extracellular components (e.g., collagen), and geometric factors to the overall resistive behavior of the ventricle.

APPENDIX

Computer Simulation of Coupled Ventricular-Arterial System

The details of the computer simulation study to assess the effects of ventricular resistance on ventricular performance are presented. The electrical equivalent network representing the left ventricle coupled to its arterial load is depicted in Fig. 9. The left ventricle and the arterial load were represented by a time-varying elastance [E(t)] in series with a pressure-dependent resistance [R(P_0)] (8, 9, 16) and a three-element modified Windkessel (30), respectively. The three elements of the Windkessel correspond to the peripheral resistance (R_p), lumped arterial compliance (C), and characteristic impedance (R_c). L (Fig. 9) represents the fluid inertia between the ventricular cavity and the ascending aorta, while the diode simulates the aortic valve.

E(t) and $R(P_0)$ were chosen to correspond to normal values for canine left ventricles (8, 9, 16, 22). E(t) was explicitly represented by a third-order polynomial in time (16), while $R(P_0)$ was a linear function of isovolumetric pressure, P_0 (9 and results of the present report). The polynomial coefficients representing E(t) were chosen so that the peak elastance and time to peak elastance were 6.11 mmHg/ml and 197 ms,

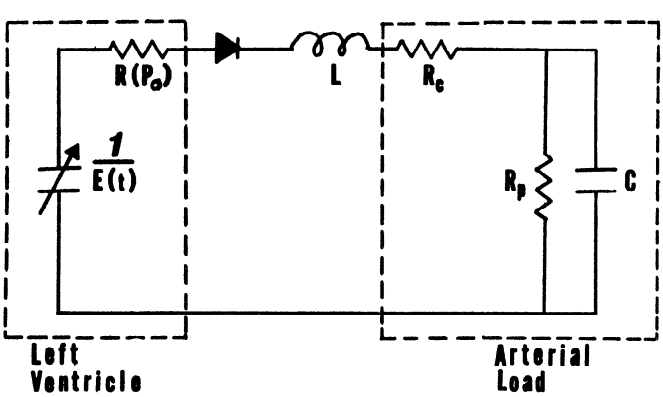


FIG. 9. Model of left ventricle and its arterial load used in simulation study. Left ventricle is represented by a time-varying elastance [E(t)] in series with a pressure-dependent resistance [$R(P_0)$]. Arterial load consists of R_p (peripheral resistance), C (lumped arterial compliance), and R_c (characteristic impedance). L, inertia of blood column in outflow tract and aorta. Diode corresponds to aortic valve.

TABLE 3. *Parameter values used for computer simulation of coupled ventricular-arterial system*

Run	R_p	C	R_c	L	Comments	
					R_p	C
1	3.3	0.40	0.1	0.0015	normal	normal
2	7.0	0.40	0.1	0.0015	high	normal
3	1.6	0.40	0.1	0.0015	low	normal
4	3.3	0.13	0.1	0.0015	normal	low
5	7.0	0.13	0.1	0.0015	high	low
6	1.6	0.13	0.1	0.0015	low	low
7	3.3	1.20	0.1	0.0015	normal	high
8	7.0	1.20	0.1	0.0015	high	high
9	1.6	1.20	0.1	0.0015	low	high

R_p, peripheral resistance (mmHg·s·ml^{-1}); C, lumped arterial compliance (ml/mmHg); R_c, characteristic impedance (mmHg·s·ml^{-1}); L, inertia of blood column in outflow tract and aorta (mmHg·s^{-2}·ml^{-1}). Left ventricular parameters include the following: elastance function [$E(t) = 0.2 + 3.75t + 418.87t^2 - 1449.18t^3$]; Resistance function [$R(P_0) = 0.0015\ P_0(t)$]; End-diastolic volume, 37 ml; Absolute residual volume (V_d), 6.0 ml; Heart rate, 120 beats/min.

respectively. These are within the normal range for a canine left ventricle at a heart rate of 120 beats/min (16). The following equations define $E(t)$ and $R(P_0)$

$$E(t) = 0.2 + 3.75t + 418.87t^2 - 1449.18t^3 \quad (A1)$$

$$R(P_0) = 0.0015\ P_0(t) \quad (A2)$$

Noting that the instantaneous isovolumetric pressure, $P_0(t)$, is simply equal to $E(t)[V(t) - V_d]$, we can rewrite *Eqs. A2* and *3* as follows

$$R(P_0) = 0.0015\ E(t)[V(t) - V_d] \quad (A3)$$

$$P(t) = E(t)[V(t) - V_d] - R(P_0)\dot{V}(t) \quad (A4)$$

where $V(t)$, $\dot{V}(t)$, and V_d are the instantaneous ventricular volume, flow out of the ventricle, and absolute residual volume (16), respectively. The end-diastolic volume [i.e., $V(t)$ at $t = 0$] and V_d were chosen to be 37 and 6 ml, respectively.

The normal values of arterial load parameters, R_p, R_c, and C were chosen to be 3.3 mmHg·s·ml^{-1}, 0.4 ml/mmHg, and 0.1 mmHg·s·ml^{-1}, respectively, which correspond to typical values observed in dogs. To study the ventricular performance at different arterial loads, R_p and C were varied to yield nine different conditions (Table 3). L was kept constant at 0.0015 mmHg·s·ml^{-1}, which corresponds to the inertia of a cylindrical blood column 1.25 cm long and 1.22 cm in diameter.

The dynamics of the system depicted in Fig. 9 was described in terms of the following three state variables. X_1, effective ventricular volume ($= V(t) - V_d$); X_2, flow out of the ventricle; and X_3, pressure drop across R_p or C.

The interrelationships among these three state variables were written in terms of the following three simultaneous differential equations

$$\dot{X}_1 = -X_2$$

$$\dot{X}_2 = \{E(t)X_1 - [R(P_0) + R_c]X_2 - X_3\}/L$$

$$\dot{X}_3 = X_2/C - X_3/R_pC$$

$E(t)$ and $R(P_0)$ were given by *Eq. A1* and *A3*, respectively. Numerical solution of these equations were obtained using the fourth-order Runge-Kutta method. The initial values of X_1, X_2, and X_3 were chosen to be 31 ml, 0 ml/s, and 70 mmHg, respectively. The numerical solution continued for multiple cycles (usually 3–5) until the aortic pressure at the beginning of the cycle was within 1 mmHg of the pressure at the end of the cycle (i.e., steady-state solution). The results presented in Fig. 8 and Table 2 are for the steady-state condition.

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